Guideline Justification

Background

Impact of Malformations

Evaluation and management of newborns with one or more malformations present a significant challenge to health care providers and families. Despite major advances in our understanding of their etiology and pathogenesis, malformations remain the leading cause of infant mortality in the United States [Guyer et al, 1995, 1997], outranking both respiratory distress syndrome and low birth weight [Kempe et al, 1997; Guyer et al, 1996]. Malformations cause 22% of neonatal deaths [March of Dimes, 1996] and 20% of post-neonatal deaths [Kempe et al, 1997]. The costs of health care for infants with congenital anomalies have been estimated to be over $6 billion annually [Rice, Hodgson & Kopstein 1985]. This figure does not include the "hidden" costs of lost wages, transportation and other non-medical issues confronting these families [Waitzman et al, 1994].

Of equal importance is the emotional burden borne by the families of children with malformations. The birth of such a child has understandably profound effects on the family, not only in terms of medical costs, but also in interpersonal dynamics [Bocian & Kaback, 1978; Nolan & Pless, 1986; Weiss, 1992; Bishop, 1993]. The infant may have unique and complex needs for health care, education and social service. Family stress [Nolan & Pless, 1986], fear of stigmatization, loss of health care coverage and genetic discrimination may be important issues for the family [Hudson et al, 1995; Lapham et al, 1996]. Families perceive malformations likely to result in early infant death or prolonged illness as being the most burdensome [Ekwo, Kim & Gosselink, 1987].

Definitions

"Malformation" is a descriptive term referring to abnormal structural development. A *major malformation* refers to a structural defect that has a significant effect on function or social acceptability, such as a ventricular septal defect or a cleft lip. A *minor malformation* is a structural abnormality that has minimal effect on function or societal acceptance, such as a preauricular ear pit or partial syndactyly (fusion) of the second and third toes. A *developmental variant* or *variation* is a cosmetically and functionally insignificant structural deviation, which can be familial and of prenatal origin, such as a minor incurving of the fifth finger or over-folding of the superior helix of the ear. *Dysmorphology* is the field concerned with physical variations and malformations and their diagnostic and clinical significance. In this document, use of the term "malformation" refers to *major* malformations, except when specified, and includes deformations and disruptions (*see Appendix 1. Glossary*).

Incidence and Prevalence of Malformations

Congenital malformations are found in 2-5% of all newborns [Myrianthopoulos, 1974; Van Regemorter et al, 1984], including some which are not of serious import; another 2-5% of infants will be found to have a malformation during the first year of life [Myrianthopoulos 1974; Christianson et al 1981]. Approximately 0.5 - 1.3% of newborns have *more than one* malformation recognized at birth [Myrianthopoulos, 1974]. *Table 1* shows the prevalence of selected malformations among newborns from the New York State Congenital Malformations

Registry. In this data set, a single malformation was found in 270/10,000 newborns; 350/10,000 had one or more malformations. Although some malformations are more common among certain racial and ethnic groups (e.g. polydactyly among African Americans or cleft lip/palate among Native Americans), malformations can and do affect all segments of the population [Christianson et al, 1981; Chavez et al, 1989].

Table 1. Prevalence of Selected Malformations in New York State 1993*

Condition	Prevalence/10,000 births
Hypospadias	32.6
Ventricular septal defect	30.8
Atrial septal defect	26.3
Congenital dislocation of hip	18.6
Obstructive uropathy	17.8
Down syndrome	10.6
Talipes equinovarus	9.8
Congenital hydrocephalus	7.7
Cleft palate	6.7

Source: New York State Congenital Malformations Registry

*72.9% of malformations reported to the Registry were identified at less than 3 days of age, 11.8% at 3-29 days and 15.3% at more than 29 days of age.

A single malformation often portends the presence of additional malformations. Nearly 4% of newborns with at least one single major malformation have additional major malformations [Edmonds, 1997]. The likelihood that additional malformations are present varies with the first malformation identified. Only 8-9% of newborns with hypospadias, for example, have associated malformations whereas 75% of newborns with a triphalangeal thumb have additional malformations (*See Table 2*). On the other hand, even major malformations which tend to be isolated are sometimes accompanied by others.

Table 2. Association of Specific Single Malformations with Additional Malformations

Condition	% with Associated Malformations	Condition	% with Associated Malformations
Hydrocephalus	70 - 80	Jejunal or ileal atresia	5
Neural tube defects	20	Atresia of colon	33
Microphthalmia/coloboma	15 - 30	Urinary tract anomalies	72
Microtia/anotia	20 - 40	Medullary sponge kidney	uncommon
Preauricular tag	5	Horseshoe kidney	33
Preauricular pit	10 - 30	Hypospadias	8 - 9
Choanal atresia	50	Inguinal hernia	uncommon
Tracheoesophageal fistula	30 - 70	Klippel Feil anomaly	more than 50
Diaphragmatic hernia	56	Limb deficiencies	32 - 53
Anorectal atresia	up to 50	Triphalangeal thumb	75
Cleft lip/palate	14 - 45	Omphalocele	40 - 88
Cleft palate	24 - 60	Gastroschisis	21 - 39
Lip pits	80	Supernumerary nipples	up to 27
Extrahepatic biliary atresia	12 - 27	Single umbilical artery	18 - 45

Minor malformations and developmental variants occur in 14 - 40% of otherwise normal newborns [Frias and Carey, 1996] and may also predict the presence of major malformations. Infants with three or more *minor* malformations have an increased risk of occult major malformations [Marden & Smith, 1964; Leppig et al, 1987], including central nervous system malformations not clinically apparent at birth [Smith & Bostian, 1964].

In addition, specific patterns of multiple *minor* malformations may be presenting signs of a genetic condition or malformation syndrome (*see Appendix 1. Glossary*), even in the absence of a major malformation. For example, a newborn with Down syndrome may have epicanthal folds, single palmar creases, small ears and other externally visible signs of the condition, yet lack a major malformation such as a congenital heart defect.

Etiology of Malformations

The causes of congenital malformations are varied; many are associated with known genetic and/or environmental factors whereas others have no known cause [Kalter & Warkany, 1983 a,b; Nelson & Holmes, 1989]. Few studies have evaluated the etiology of malformations in newborn populations and inclusion criteria have varied; some studies include all genetic conditions within the definition of a malformation whereas others consider only structural malformations. The paucity of data leaves us with a broad range of estimates regarding the various etiologic categories. Among a population of 10,000 consecutive live births, using birth records, Van Regemorter et al [1984] identified 1.7% with major malformations; of these, 12 (7%) had Mendelian conditions, 23 (13%) had chromosomal disorders, 89 (51%) had single malformations with multifactorial inheritance and 50 (29%) had one or more malformations of unknown or unclear etiology. Nelson and Holmes [1989] reviewed birth records of 69,277 deliveries of at least 20 weeks gestation and found 2.24% had at least one major malformation; of these, 10.1% had chromosomal anomalies, 3.1% had Mendelian disorders, 23% had malformations with multifactorial inheritance, 14.5% had "familial" conditions, 3.2% had teratogenically induced malformations, 2.9% had other causes (such as intrauterine factors) and 43.2% had an unknown cause. On the other hand, Kalter and Warkany [1983 a,b] opined that 7.5% of congenital malformations had a monogenic (Mendelian) basis, 6% were due to chromosomal anomalies, 5% were due to maternal infections, illnesses such as diabetes and medications such as phenytoin and 20% were multifactorial; known causes accounting for only 38.5% of all malformations. In summary, these and related studies would indicate that 3 - 8% of malformations have a Mendelian cause, 6 -13% are due to chromosomal anomalies, 20 - 51% are multifactorial, and 29 - 61% are of unknown etiology.

Importance of Specific Diagnosis

Many newborns with multiple malformations have recognizable patterns referred to as "syndromes" *(see Appendix 1. Glossary*). Some diagnoses are relatively straightforward and common enough to be easily recognized without outside specialty consultation. These include some of the chromosomal disorders such as Down syndrome, multifactorial conditions such as neural tube defects and Mendelian disorders such as achondroplasia. At times, even these conditions can be difficult to identify in the neonate. Malformations may occur together in a non-random *association* without a specific recognizable cause; several well documented associations of three or more malformations are known, such as VATER (*v*ertebral,

*a*nal, *t*racheo-*e*sophageal and *r*adial or *r*enal defects) and CHARGE (*c*oloboma of the eye, *h*eart, *a*tresia of choanae, growth or developmental *r*etardation, *g*enital and *e*ar defects) (*see Appendix 1. Glossary*). For some malformation patterns, certain clinical features evolve with age or time. A newborn believed to have a single isolated malformation may have an underlying syndrome which is not apparent in the newborn period.

Timely identification of associations and syndromes in the newborn period may enable the clinician to anticipate otherwise unforeseen complications [Wardinsky, 1994], resulting in improved outcome *(see Table 3)*. For example, recognition that a newborn with cleft palate has an airway problem due to Pierre Robin sequence (cleft palate, micrognathia and glossoptosis) can lead to appropriate management of the problem, resulting in relief of failure to thrive [Shprintzen, 1992]. In another example, recognition that a newborn with edema has coarctation of the aorta associated with Turner syndrome can lead to appropriate management and relief of cardiorespiratory symptoms [Hall, 1988].

Table 3. Selected Malformation Syndromes in Which Early Diagnosis Impacts Management

DISORDER	IMPACT
Down syndrome	Early recognition/treatment of congenital heart disease or late-onset hypothyroidism
Trisomy 18	Recognition of poor prognosis allows appropriate counseling and treatment decisions
Achondroplasia	Accurate diagnosis permits monitoring for cervical spinal compression and hydrocephalus
Beckwith-Wiedemann syndrome	Early management of hypoglycemia and surveillance for tumors
Congenital adrenal hyperplasia/ ambiguous genitalia	Prevention of adrenal insufficiency; optimal gender assignment
Williams syndrome (7q11 chromosomal deletion)	Early recognition of congenital heart disease; management of hypercalcemia
Velocardiofacial syndrome/DiGeorge sequence (22q11 deletion)	Early monitoring of immune deficiency, congenital heart defects, cleft palate, hypocalcemia
CHARGE association	Early recognition of hearing and visual deficits; early recognition of airway compromise

Conversely, delayed or inaccurate diagnoses may compromise optimal care, limit anticipation of complications and timely intervention, and negatively impact outcome. For example, failure to recognize achondroplasia and its potential complications may result in early pulmonary insufficiency [Reid et al,1987] or cervico-medullary cord compression [Pauli et al, 1984]. Life threatening hemorrhage may occur in a newborn with absent radii due to thrombocytopenia-absent radius (TAR) syndrome if an elective surgical procedure (even circumcision) is performed without a platelet count in the mistaken belief that the malformation is isolated [Adeyokunni, 1984]. A newborn with ambiguous genitalia due to congenital adrenal hyperplasia may develop life-threatening adrenal insufficiency before the diagnosis is considered [Lebovitz RM, 1984; Allen et al, 1997].

Long-term planning for any infant with a special health care need is based on prognosis for cognitive development, physical functioning and anticipated medical complications. However, among the hundreds of multiple malformation syndromes already known [Jones, 1996], there is wide variability in developmental, functional and medical outcomes. Thus, for the newborn with one or more malformations, plans for education, anticipation of functional needs and reduction of medical morbidity may vary according to the specific diagnosis and its spectrum of outcomes (variability) and natural history [Wardinsky, 1994]. Hall [1988] emphasized the value of natural history studies and described a reciprocal relationship between diagnosis and natural history: making a diagnosis enables natural history to be anticipated and observation of natural history may enable a diagnosis to be made.

Descriptions of the Evaluation Process

Numerous reviews describe an expert's approach to the evaluation of the newborn with congenital anomalies [Wilson, 1987; Davenport, 1990; Wardinsky, 1994; Aylsworth, 1992; Saal and Rosenbaum, 1988; Scheuerle, 1994; Chen, 1994; Lubinsky, 1983; Hall, 1988; Hall, 1993; Aase, 1992]. Each of these authors emphasizes the need to gather appropriate historical data, including prenatal, perinatal and family history. In addition, it is necessary to perform a comprehensive physical examination and carry out appropriate laboratory testing when indicated in order to assign a diagnosis (where possible) and corresponding prognosis and recurrence risks for parents and other relatives. Some authors describe the detailed physical examination necessary for the newborn with one or more malformations [Aase, 1992; Lubinsky, 1984] whereas others emphasize the observational skills necessary to recognize abnormalities of symmetry, contour, size and proportion [Hall, 1993]. A careful, systematic evaluation, measurements of unusual findings, photographic documentation and parental examination are particularly emphasized [Hall, 1988]. Some authors provide lists of findings in the history or physical examination that should prompt closer evaluation [Hall, 1988; Wardinsky, 1994; Saal & Rosenbaum, 1988; Scheuerle, 1994] and several provide algorithms for the evaluation [Wilson, 1987; Aase, 1992; Hall, 1988]. Examples of two such algorithms are shown in *Figures 3A* and *B*.

Historical Outcome Data

Population-based studies evaluating specific, objective benefits of comprehensive evaluation to the *individual* health of newborns with malformations are generally lacking. Such studies are needed and should consider the broad spectrum of severity and complexity of malformations in their analysis. In their absence, expert opinions regarding the benefits of comprehensive evaluation are based on a consistent body of anecdotal reports and accumulated clinical experience. On the other hand, relevant data are available regarding the value of specific diagnosis to *families*, primarily in assignment of recurrence risk and clarifying reproductive options, including prenatal diagnosis.

Recurrence Risk Assessment

Several studies of specific populations underscore the importance of etiologic diagnosis for genetic counseling, assisting families in reproductive planning and decision-making for prenatal diagnosis [Lubs, 1979; Rollnick & Pruzansky, 1981; Sorenson et al, 1981; Van Regemorter et al, 1984; Shprintzen et al, 1985; Jones, 1988; Nelson & Holmes, 1989]. Lie et al [1994] and Nelson and Holmes [1989] showed that even in the absence of a previously positive

Figure 3A. After Hall JG. When a child is born with congenital anomalies *(Contemp Ped* 1988 (August): 78-87, with permission).

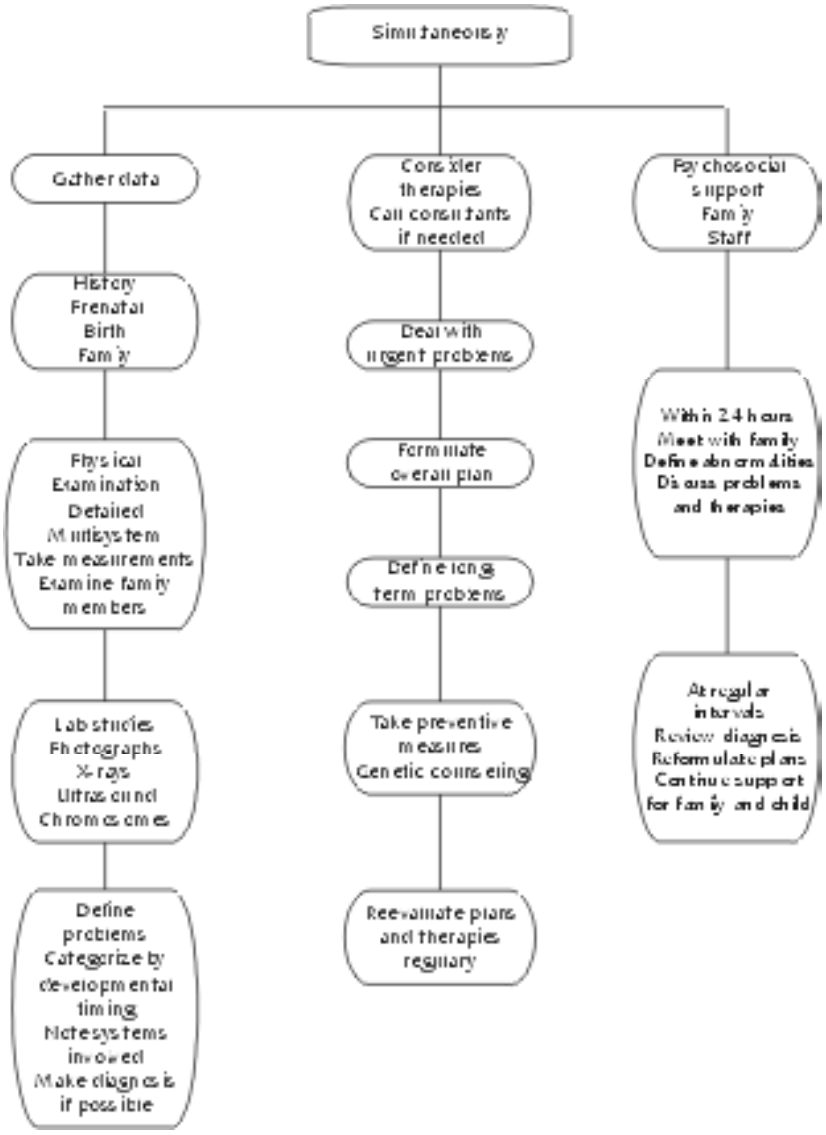
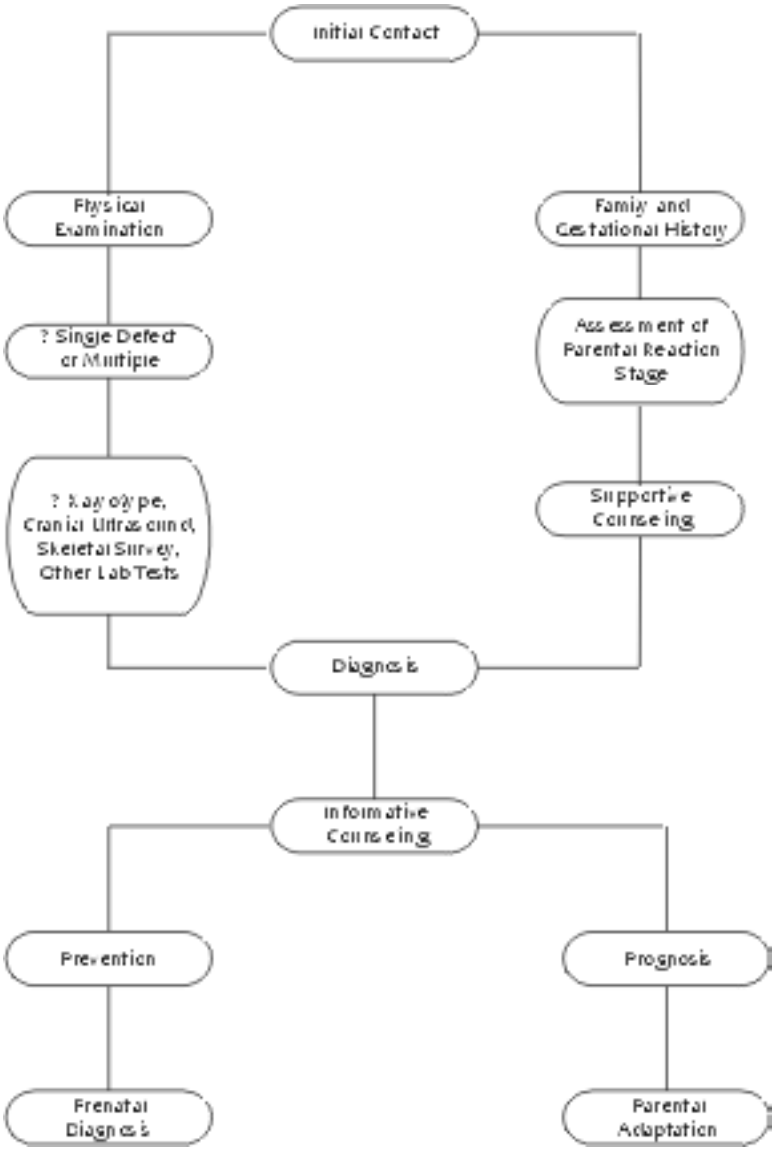


Figure 3B. After Wilson GN. The child with birth defects: Medical diagnosis and parental counseling (*Resid Staff Phys* 1987: 33 (1): 96-102, with permission).



genetic family history, the birth of a newborn with a congenital malformation increased risks for a subsequent affected sibling. Moreover, Van Regemorter et al [1984] observed that among newborns with unselected congenital anomalies, 78% had conditions with a familial recurrence risk greater than 1% and 9% had a recurrence risk greater than 10%.

Even when a diagnosis is established, genetic risk estimation is complicated by etiologic heterogeneity, including both genetic heterogeneity (mutations in different genes responsible for the same clinical phenotype)[Wilkie et al, 1994] and the existence of phenocopies, e.g. clinical patterns which mimic genetic disorders but are due to environmental factors. Genetic heterogeneity is observed in many malformation syndromes, including Saethre-Chotzen, in which some families have a mutation in the TWIST gene and others have a mutation in the FGFR3 gene [Rose et al, 1997]. One example of a phenocopy is thalidomide embryopathy, in which limb malformations mimic those seen in Roberts syndrome, a disorder characterized by autosomal recessive inheritance [Smithells & Newman, 1992]. Some disorders where etiologic heterogeneity has been observed include: neural tube defects, which can be due to Mendelian, chromosomal, teratogenic or multifactorial etiologies [Holmes et al, 1976]; osteogenesis imperfecta, in which both dominant and recessive varieties can present in the newborn period (an example of *genetic* heterogeneity) [Sillence, 1986]; and the hemifacial microsomia spectrum in which local vascular disruption, chromosomal abnormality or a dominant gene all lead to similar ear anomalies [Gorlin, 1996, p. 646].

Intent of the Guideline

Few clinical guidelines exist to assist the primary care provider or specialist in the approach to diagnosis and initial management of the newborn affected with a single or multiple malformations. Guidelines for anticipatory management of certain malformations and syndromes are available [American Academy of Pediatrics, 1997] but are not focused on the initial process before diagnosis is made. These issues can be critical for the neonate with life-threatening anomalies, for whom rapid decision-making may be imperative, but may be equally important for the newborn who is not critically ill.

This Guideline describes essential components of the diagnosis and evaluation of newborns with one or more malformations for health care providers who care for newborn infants, irrespective of specialty orientation, with intent to facilitate specific diagnosis and appropriate counseling and management. Although many of the components reflect general practice, some aspects require greater emphasis in this setting. For purposes of completeness, a comprehensive process is described.

The Guideline was developed in response to the perception that some newborns with congenital malformations receive inadequate evaluation while others are inappropriately or excessively investigated. There is scant population-based evidence in support of this contention, but many anecdotal reports support it. In addition, it is also perceived that families frequently receive sub-optimal counseling [Kenen & Smith, 1995; Shapiro, 1993; Walker, 1996]. Family surveys indicate preferences for a family-centered approach involving ongoing relationships with primary care providers [Black & Weiss, 1988; Krahn, 1993; Sharp et al, 1992; Ptacek, 1996].

Positive outcomes expected from the use of this Guideline include a more consistent approach to assessment, better use of resources with improved cost-benefit, improved determination of prognosis, better management of affected newborns and their families, better preparation of families for reproductive planning and heightened family satisfaction and adjustment. The orderly process described in the Guideline includes components which should be part of the evaluation of any newborn with one or more congenital anomalies, but does not specify an inflexible sequence, recognizing that evaluation involves repeated synthesis and modification of the process as information is gathered. It is hoped that this Guideline will help health care providers to better evaluate these newborns or to decide when to refer them for more specialized care.

Sources for Referral and Consultation:

New York State Genetic Service Providers, *Appendix 4*
American College of Medical Genetics (301) 530-7127
National Society of Genetic Counselors (610) 872-7608, mail box #7
State Genetics Coordinators, *Appendix 5*
March of Dimes Birth Defects Foundation (914) 428-7100
New York State Genetic Services Program (518) 486-2215
Organization of Teratology Information Services (801) 328-2229
New York State Developmental Disabilities Council (800) 395-3372

The Guideline is intended to cover common situations; providers need to assess their personal level of comfort and expertise as well as their practice setting when evaluating more complex cases. If significant components of the process cannot be accomplished by the primary care provider, referral should be made to a specialist in medical genetics (*see sidebar*).

Table 4. Organizations Represented on the Clinical Guidelines Team for Evaluation of the Newborn with Single or Multiple Congenital Anomalies*

Alliance of Genetic Support Groups
American Academy of Family Physicians
American Academy of Pediatrics, New York State Chapter
American College of Medical Genetics
American College of Obstetrics and Gynecology
American College of Physicians, New York State Chapter
American College of Surgeons
American Public Health Association, New York State Affiliate
Council of Regional Networks for Genetic Services
International Society of Nurses in Genetics
Links, Inc.
March of Dimes Birth Defects Foundation
National Society of Genetic Counselors
New York State Task Force on Life and the Law
Organization of Teratology Information Services
Society of Craniofacial Genetics

** see Appendix 8 for further information about each organization*

The recommendations were developed by an interdisciplinary task force convened under the sponsorship of the New York State Department of Health and the American College of Medical Genetics Foundation, including representatives from Family Medicine, Pediatrics, Obstetrics, Medical Genetics, Pediatric Surgery, Public Health and consumer groups (see *Table 4* for participating organizations). The Guideline is based on a review of the available literature and a consensus of expert opinion, with the recognition that evidence-based literature in this area is limited.

Components of Evaluation and Care (*see Figure 2*)

When a newborn infant with one or more malformations is identified, a detailed history and physical examination must be undertaken to ascertain whether additional malformations are present and to seek a specific etiologic diagnosis if possible. Essential components of the history and physical examination of the affected newborn include a detailed prenatal, perinatal and family

Figure 2: Components of Evaluation and Care Reference Card

Components of Evaluation and Care Reference Card
American College of Medical Genetics

Evaluation of the Newborn with Malformations

Components of Evaluation and Care

History

- Prenatal
  - Maternal age, parity, health
  - Complications of pregnancy
  - Illnesses and treatments
  - Exposures (drugs, etc)
  - Folic acid supplementation
  - Prenatal testing
- Perinatal
  - Duration of pregnancy
  - Intrapartum course
  - Presentation and mode of delivery
  - Complications and course
- Family history
  - Information re: three generations
  - Malformed infants
  - Stillborns
  - Familial disorders or traits
  - Consanguinity
  - Ethnic background

Physical Examination

- Gestational age, growth parameters and measurements (%iles)
- Comprehensive examination
  - General appearance
    - Proportionality and symmetry
    - Positioning, posture
    - Behavior
    - Other observations
  - Skin pigmentation, dimples, peeling, vascular or other lesions
  - Head shape, symmetry, fontanelles
  - Scalp hair patterning and whorls
  - Facial features
    - Pupils, orbits, palpebral fissure length and slant
    - Ear rotation, size and shape
    - Nasal appearance and patency
    - Lips, philtrum and vermilion border
    - Palate, tongue and alveolar ridges
    - Mandibular shape and size
  - Nuchal posterior hairline, redundant skin or webbing, sinus tracts
  - Chest shape, symmetry, location of nipples, +/- accessory nipples
  - Heart murmurs and pulses
  - Lung sound symmetry

Components of Evaluation and Care Reference Card
New York State Department of Health

Physical Examination (continued)

- Abdominal wall and palpation abnormalities, e.g. masses
- Genital appearance and maturation
- Anal orifice location and patency
- Back symmetry +/- sinus tracts or hair tufts in intergluteal cleft
- Extremity proportion, appearance, range of motion, abnormalities
  - Palmar creases, flexion creases at joints
- Neurological exam, including tone, alertness & reflexes

Initial Impression & Differential Diagnosis

- Single (isolated) malformation
- Multiple malformations of known pattern (syndrome identified)
- Multiple malformations (pattern not recognized)

Diagnostic Evaluation

- Imaging
- Chromosomal analysis
- Other genetic tests
- Consider specialty referral and/or consultation

Develop Working Diagnosis and Counsel Family

Counseling the Family

- Counseling principles
  - Supportive
  - Respect privacy and confidentiality
  - Facilitate grieving process
- Supportive setting
  - Privacy and quiet
  - Inclusion of others according to family preference
- Content
  - Medical facts and diagnoses
  - Etiology and prognosis
  - Treatment plan and priorities
  - Uncertainties
  - Resources
  - Recurrence risks
  - Family psychosocial support

Longitudinal Care and Case Management

- Written reports and written materials for families
- Ongoing care and referrals as indicated

history, a review of pertinent medical records, and a complete physical examination of the newborn, focused on identifying structural abnormalities beyond the sentinel defect [Wilson, 1987; Davenport, 1990; Wardinsky, 1994; Aylsworth, 1992; Saal and Rosenbaum, 1988; Scheuerle, 1994; Chen, 1994; Lubinsky, 1983; Hall, 1988; Hall, 1993; Aase, 1992].

The sequence described suggests an orderly passage from history to physical examination to diagnostic evaluation. However, in actual practice, the history and physical examination represent a dynamic and interactive process in which certain elements of the history may follow the physical exam and certain physical parameters may be assessed based on information derived from historical data. Likewise, results of initial diagnostic testing may suggest the need for additional history or physical assessment.

The comprehensive history and physical examination outlined herein may yield a specific etiologic diagnosis [Hall, 1993]. Among those for whom a diagnosis remains unknown, some have extremely rare patterns of malformation recognizable only to a few experts, whereas others have unique patterns, newly recognized, unpublished or undocumented syndromes or subtle presentations of known conditions which may become more recognizable with maturity. A significant percentage, even when seen by multiple experts, will remain undiagnosed. Shprintzen [1985] and Cohen [1978] examined patients at treatment centers for craniofacial malformations; up to 40% of patients with multiple malformations had unknown or new conditions. In infants with multiple malformations other than craniofacial, such percentages are undetermined and may be significantly lower.

It is not uncommon for parents or other relatives of the affected newborn to be cited as having similar features or subtle variations of development reminiscent of the affected newborn. In some cases, these will prove to be families with familial variations or signs of inherited conditions; at other times, the observation will be the result of a family's understandable denial and desire to minimize the significance of the problem. Clinical examination of other reportedly affected individuals in the family should be performed for clarification when possible.

History

The prenatal, perinatal and family history often provide clues as to underlying etiology and pathogenesis. Medical records should be reviewed to confirm any significant positive findings derived from history. Record review may reveal that an etiologic diagnosis has already been made in a relative or may reveal a pattern of anomalies among family members which will suggest a specific diagnosis. The following elements should be included in the history:

Prenatal history

- Maternal age, parity and health, including maternal illnesses

  Relevant positive findings include maternal age over 35 (a risk factor for trisomy), a history of miscarriage or maternal illnesses (or their treatments) which predispose to some congenital anomalies. This includes maternal conditions such as lupus, diabetes, epilepsy and phenyl-ketonuria.

- Onset and quality of fetal movements throughout pregnancy

  Several syndromes and some neuromuscular disorders are characterized by decreased fetal activity. Sudden diminution of activity may be significant and diagnostically helpful.

- Pregnancy complications

  A history of bleeding, hypertension, placental abruption, threatened abortion, abdominal pregnancy, multiple gestation, maternal battering, etc. may suggest etiologies for poor fetal growth or for congenital anomalies related to fetal vascular insufficiency (see *"Disruption"* in *Appendix 1. Glossary*).

- Viral and parasitic illnesses

  Infections with cytomegalovirus, rubella, varicella, toxoplasmosis or parvovirus may be associated with congenital anomalies.

- Teratogenic exposures

  Alcohol, anticonvulsants, isotretinoin, thalidomide, warfarin and a variety of other agents are proven causes of congenital malformations. Others such as cocaine have been implicated but not proven to cause birth defects. When considering the possibility that an exposure is responsible for malformations, it is important to consider gestational age at exposure, dose and possible interaction with other maternal factors, such as maternal illness [Gorlin et al, 1990, p.15].

- Periconceptional supplementation with folate

  Folic acid supplementation has been shown to reduce both recurrence and occurrence of certain malformations, such as neural tube defects and cleft lip/palate. However, supplementation does not eliminate the risk for these malformations, suggesting that some are folate insensitive. This distinction may be of value in formulating the differential diagnosis and in assessment of recurrence risk.

- Previous testing during pregnancy

  Results of amniocentesis, chorionic villus sampling or high resolution ultrasound, for example, may point to or limit some diagnostic considerations, such as chromosomal anomalies, or major internal malformations, such as renal abnormalities.

Perinatal history

- Duration of pregnancy

  Gestational age should be assessed by comparing data from maternal history (last menstrual period or expected date of delivery) with obstetrical estimates, based on ultrasound measurement. Some physical findings are less apparent in preterm infants. Conversely, some abnormal findings in the term newborn, such as non-palpable testes, can be normal findings in the preterm newborn.

- Presentation and mode of delivery

  Joint position and cranial contour can be affected by intrauterine mechanical forces which alter the space available for fetal movement; in addition, some conditions, such as myelomeningocele, hydrocephalus and neuromuscular disorders, may predispose to breech position.

- Intrapartum course
- Intrapartum drug or medication exposure
- Complications of delivery and infant's condition at birth (Apgar score)

- Description of placenta

  This information allows interpretation of the condition of the newborn with malformations who presents with abnormal neurological findings, in light of possible complicating intrapartum events. Placental abnormalities such as infarcts may be relevant to diagnostic considerations.

- Neonatal course

  An atypical clinical course may focus evaluation for occult malformations not otherwise considered. Special attention should be paid to documentation that the newborn has passed urine and meconium and, if stable, has taken a feeding. Failure to pass meconium may prompt evaluation for cystic fibrosis, high anal atresia or Hirschprung disease. Vomiting may prompt consideration of such anomalies as tracheoesophageal fistula or duodenal atresia, but may also suggest inborn errors of metabolism presenting with malformations (example: glutaric acidemia II).

Family History

Family history is an essential part of the evaluation of the newborn with malformations. Many major malformations have a strong genetic component. While most families at first report a negative history of malformations, it is not uncommon to learn after further discussion that a sibling or cousin had a similar malformation. Positive responses to family history questions should be confirmed, when possible, by review of medical records (with appropriate consent) or verification by relatives. Contact with relatives is best initiated by the family. Family photographs can be of particular value.

Information about three generations (siblings, parents, aunts and uncles, cousins and grandparents) is essential; a formal pedigree is optimal [Bennett et al, 1995] (*see Figure 4*). The degree of detail and areas of emphasis in the family history should be based on the complexity and type of congenital anomaly in the affected newborn. For example, if the newborn has an apparently isolated limb defect (such as an extra digit), questions should not only focus on limb defects in other family members, but should include inquiry about other malformations, thereby potentially identifying the spectrum of phenotypic variability in a genetic syndrome. Conversely, a positive finding in the history may warrant more comprehensive examination of certain physical parameters. For example, a history of maternal low grade fever and rash (suggesting maternal rubella) would prompt critical evaluation of hearing in a child with apparently isolated microcephaly. If there are positive responses indicating the possibility of familial malformations, consultation with a medical geneticist may be of value.

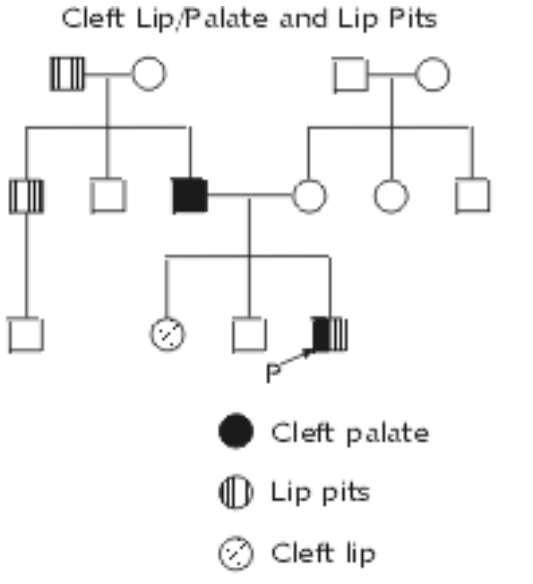
Areas of inquiry should include:

- A three generation family history (*see Figure 4*), noting health information about all relatives, including siblings, parents, grandparents, uncles, aunts and cousins and noting any instances of reproductive losses or infertility

  A detailed pedigree may uncover a history of congenital malformations or variations which were not recognized as such by the family. Examples such as altered head shape, extremes of stature and learning disabilities may be signs of genetic conditions relevant to the newborn being evaluated. A history of reproductive loss or infertility may be related to malformations which caused early fetal loss, sometimes associated with balanced chromosomal translocation in either parent. Alternatively, infertility may be a manifestation of malformations of reproductive organs.

Figure 4. A Positive Family History in a Newborn with Cleft Palate.

The newborn infant (indicated by the arrow and letter P [for *proband*]) had apparently isolated cleft palate on initial examination. His father had cleft palate and his older sister had cleft lip. Examination of additional family members revealed the presence of lower lip pits. Repeat examination of the newborn revealed that he also had lip pits. This pattern of malformations is diagnostic for the autosomal dominant lip pits (van der Woude) syndrome. The illustration below demonstrates the value of careful examination of family members when there is a positive family history of malformations.



*See Glossary (Appendix 1) for key to symbols

- Infants in the immediate or extended family with malformations or birth defects

  Many congenital anomalies have a genetic basis. In addition, some patterns of anomalies are sufficiently variable that they present differently among affected family members. Accordingly, there should be documentation of malformations in previously affected family members, even if not identical to those of the affected newborn.

- Neonatal deaths, stillbirths or childhood deaths in immediate or extended family

  Some neonatal deaths or stillbirths may not have been examined for malformations; caution should be taken in drawing conclusions from a positive or negative response unless an etiology has been determined and/or there are pre- and/or post-mortem records to review.

- Familial disorders or physical features that "run in the family"

  At times, it may be difficult to distinguish familial variations noted in a newborn from variations or minor anomalies suggestive of a malformation syndrome. Photographs of allegedly affected relatives may be particularly valuable.

- Consanguinity in parents

  Consanguinity in parents may increase the risk for rare recessive disorders, including some associated with malformations, such as Seckel syndrome.

- Ethnic background

  Some malformations are more common in specific racial and ethnic groups, such as spina bifida in those of Celtic background. In addition, some ethnic groups such as the Amish have a greater prevalence of consanguinity due to a smaller population, custom or geographic isolation. Finally, ethnic background may define certain physical findings as normal, such as the typical canthal folds of some Asian populations.

- Prior genetic testing or screening

  Include information on genetic testing or screening performed on relatives, if available. This information may increase or decrease consideration of specific diagnoses for the neonate being evaluated.

Physical Examination

As mentioned previously, a thorough physical examination of the newborn may be carried out prior to obtaining a comprehensive history. Doing so may facilitate familial interaction and focus aspects of the history taking on those most relevant to the defined problem. In all instances, however, a complete physical examination must be done, with particular attention to both internal and external congenital anomalies and to physical variations which might be indicative of abnormal development [Wardinsky, 1994]. In the presence of a major anomaly, minor anomalies and variations assume greater significance and may lead to a diagnosis otherwise not considered. For example, hypoplasia of the nipples in a male newborn may be of greater significance in the presence of total alopecia, suggesting ectodermal dysplasia. Moreover, a pattern of multiple minor malformations may lead to a diagnosis of a specific malformation syndrome, even in the absence of a major malformation. A single sign or anomaly should not be considered pathognomonic for any specific disorder; rather, it is the overall pattern of findings which suggests a particular diagnosis.

Measurement of length, weight and head circumference should be routine, with notation of percentiles on standard charts for newborns of different gestational ages (*Appendix 2*). Additional measurements are indicated when disproportion or asymmetry are noted in the newborn. Normative data for such parameters as upper/lower segment ratios, inner canthal distance and others are available in *Appendix 2*. Photographs of abnormal findings (with appropriate consent) are often valuable, especially to document physical findings which may change over time.

The following description lists essential components of the newborn physical examination along with reasons for examining each area. The examples are not intended to be comprehensive but illustrate some of the abnormal findings which may be identified in a detailed examination. Each syndrome mentioned with reference to a specific physical finding also involves other major or minor malformations, comprising a distinctive and recognizable pattern. When a specific abnormal physical finding is identified, the clinician may wish to refer to the relevant section of this document for a brief orientation to possible syndromic causes. The full spectrum of the malformation pattern can then be reviewed in one of the referenced texts (e.g. Jones, 1997).

Growth parameters

- Assessment of gestational age by physical parameters *(see Appendix 2A*)
- Length, weight and head circumference, with percentiles (*see Appendix 2B*)
- Assessment of proportionality/symmetry
- Specific measurements as indicated by observation (*see Appendices 2C-J*)

Assessment of gestational age is an essential adjunct to interpretation of physical findings in the newborn. Tone, activity, skin condition, hair pattern and external physical features such as ear cartilage and nipple development, for example, will vary with gestational age. Certain malformation syndromes, such as Down syndrome, may result in physical findings, such as tone and nipple development, that are discordant with actual gestational age.

Excessive growth may suggest the fetal effects of maternal diabetes or other overgrowth syndromes such as Beckwith-Wiedemann syndrome. Birthweight of newborns with generalized edema is also increased; the differential diagnosis for edema is complex and includes cardiovascular, hematologic, metabolic and infectious disorders. Growth retardation is present in a large number of malformation syndromes, including fetal alcohol syndrome and chromosomal disorders such as trisomies 18 and 13.

Visual inspection should be undertaken to look for bilateral symmetry and proportionality. If asymmetry is suspected, detailed measurements should be done for confirmation. For example, if the limbs appear abnormally short or long, there should be measurement of the upper to lower segment ratio (*Appendix 2C*). If the eyes appear widely spaced, then inner and outer canthal distance should be measured (*Appendices 2D and 2E*).

Measurements of physical findings which appear disproportionate are important for several reasons. Measurement will confirm or deny the visual impression. In addition, at times, apparently abnormal findings may be illusionary, such as the appearance of widely spaced eyes in the presence of a depressed nasal bridge.

General appearance

This observational component of the physical examination is essential. Such parameters as tone, posturing, positioning, alertness, vigor, color, symmetry, proportionality and respiratory effort may be critical indicators of general well-being as well as possible indicators of specific abnormalities involving internal organ system function.

Detailed examination

- Skin - pigmentation pattern (areas of increased or decreased pigmentation), dimples, vascular or visible lesions, or excessive peeling

  The neonate with one or more malformations should have a complete, unclothed examination of the skin. A thorough examination of the skin should look for vascular, macular and continuity defects, which may suggest particular syndromes. For example, facial capillary hemangiomas are seen in Beckwith-Wiedemann syndrome and a number of other malformation disorders. A port wine stain of the supraorbital region should prompt consideration of Sturge-Weber sequence. Swirling or mottled skin pigmentation may be observed in newborns with Hypomelanosis of Ito, often

associated with chromosomal mosaicism. Newborns with neurocutaneous disorders, such as neurofibromatosis and tuberous sclerosis, are sometimes observed to have hyper and/or hypo-pigmented macules at birth. Defects of skin continuity, such as those seen on the occiput in trisomy 13, can also occur in other conditions such as aplasia cutis congenita. Excessive peeling of skin in the newborn may be due to congenital epidermolysis bullosa or non-genetic etiologies, such as congenital syphilis. A linear vesicular eruption in an apparently healthy female may represent the first stage of incontinentia pigmenti.

- Head - shape, symmetry, fontanelles

  Cranial molding, including overriding or ridging of sutures, occurs frequently in newborns. It may be difficult to distinguish from abnormal cranial contour which will not resolve. Deviations from the expected head shape should be monitored for several weeks before it is concluded that an abnormal contour will persist. Persistently abnormal cranial contour suggests craniosynostosis or, occasionally, underlying central nervous system abnormalities. Unduly large or small fontanelle(s) may also be an important clue to the possibility of craniosynostosis, hydrocephalus or central nervous system malformations.

  Abnormal fontanelles may occasionally suggest disorders of bone formation or metabolism, such as cleidocranial dysplasia, osteogenesis imperfecta or hypophosphatasia. Macrocephaly or a prominent forehead may be suggestive of specific syndromes, such as achondroplasia. Microcephaly is seen in a number of syndromes, including Brachmann-de Lange syndrome and Rubinstein-Taybi syndrome.

- Scalp - hair pattern and location of hair whorls

  Variations of hair pattern, such as a double whorl or a frontal upsweep, are sometimes helpful in delineating a malformation pattern. Unusual hair whorl patterns may occur in babies with central nervous system malformations and are sometimes associated with chromosomal abnormalities such as trisomy 13.

- Facial Features
  - Eyes - pupils, orbits, including palpebral fissure inclination and length, fundi

    Some malformation syndromes result in characteristic minor malformations of the lids and fissures, such as upslanted palpebral fissures or epicanthal folds. Some lid malformations are suggestive of specific disorders, such as notching of the lower lid in Treacher Collins syndrome.

    Examination of the pupils may reveal signs of anterior chamber malformations, such as maldevelopment (coloboma) of the iris. An enlarged corneal diameter may be the first clue to congenital glaucoma; early detection may preserve vision. A white pupil may be the presentation of a congenital retinoblastoma or an anterior chamber malformation. Microphthalmia is associated with a number of syndromes, including trisomy 13. Dilation of the pupils to examine the fundi may be particularly important when eye defects are suspected.

    True hypertelorism is generally considered a radiographic diagnosis, except when extreme. Telecanthus (widely spaced inner canthal borders) can be confirmed by direct clinical measurement with a measuring tape [Jones, 1997]. These findings may be suggestive of specific syndromes, such as Opitz-Frias G/BBB (hypertelorism-hypospadias) syndrome. Hypotelorism is suggestive of the holoprosencephaly spectrum (*see Appendix 2D*).

- Ears - location, rotation, configuration and size

  Minor ear malformations may be helpful in delineating specific syndromes. Small, round ears and overfolding of the superior aspect of the pinnae are characteristic of Down syndrome; low placement of the ears is frequent in trisomy 18. Major ear malformations are seen in a number of cran-

iofacial syndromes, such as Treacher Collins syndrome and hemifacial microsomia. Hearing loss should be suspected when a major ear malformation is present. Preauricular tags, pits or sinuses may occur in isolation but may also occur in specific syndromes; when isolated, they are only occasionally associated with hearing loss. Renal malformations are not specifically associated with preauricular tags, except in certain malformation syndromes such as branchio-oto-renal syndrome, an autosomal dominantly inherited condition [Gorlin et al, 1990, p. 657].

- Nose - appearance and patency of nares; appearance of nasal bridge and columella

  Minor malformations and variations in the contour of the nares are characteristic of certain syndromes. Anteverted nares are seen in many conditions, including Williams and Robinow syndromes. Hypoplasia of the nares is seen in Johanson-Blizzard and velocardiofacial syndromes, among others. Choanal atresia is a feature of CHARGE association and can also occur in other patterns of malformation.

  Flattened nasal bridge is associated with a number of bone dysplasias, such as achondroplasia, and is also seen in many other patterns of malformation, such as Noonan syndrome. Prominent nose is a feature of Rubinstein-Taybi syndrome and Seckel syndrome, among others.

- Mouth - appearance of upper lip, philtrum and vermilion border; intra-oral examination of palate, alveolar ridges and tongue size

  Cleft lip and palate are associated with over 250 different conditions [Cohen, 1978; Gorlin et al, 1990, p.698]. Variations in the size and shape of the upper lip and philtrum are characteristic of many syndromes. A flattened upper lip (smooth philtrum) and thin vermilion border are common in fetal alcohol syndrome. Mounds or pits of the mucosa of the lower lip are frequent in van der Woude syndrome as well as several other conditions. Macrostomia (large mouth) suggests but is not specific for Goldenhar syndrome and related conditions. Macroglossia is seen in Beckwith-Wiedemann syndrome and congenital hypothyroidism.

- Mandible - shape and symmetry

  While micrognathia may be associated with isolated Pierre Robin sequence, it is also seen in a number of other malformation patterns, including bone dysplasias (such as diastrophic dysplasia and campomelic dysplasia), craniofacial syndromes (such as Treacher Collins and Stickler syndromes) and chromosomal disorders.

  Enlarged mandible (macrognathia) is rare in newborns. An apparent jaw enlargement in a newborn can be caused by hypoplasia of the maxilla (midfacial hypoplasia), which is seen in a variety of syndromes.

- Neck - posterior hairline, presence of sinus tracts, torticollis, redundant skin or webbing

  Redundant nuchal skin or webbing of the neck may be the result of a prenatal cystic hygroma which has receded. This finding should lead to consideration of Turner syndrome, Noonan syndrome or chromosomal disorders other than Turner syndrome, such as Down syndrome. Low posterior hairline with or without a broad neck may be a residuum of a cystic hygroma, but may also be an indication of shortened cervical vertebral column, due to cervical fusions, shortened cervical vertebrae or missing segments.

  Cervical sinus tracts may be isolated branchial cleft remnants or may be associated with other craniofacial anomalies.

- Chest - shape, symmetry, circumference, location of nipples, accessory nipples

  Unusual shape or symmetry of the chest wall should prompt an evaluation for malformations of the ribs or spine. These may be isolated malformations or may be part of a syndrome, such as a bone

dysplasia. Small chest circumference may occur in Down syndrome as well as many bone dysplasias. Deficiency of pectoralis muscles and abnormalities of breast tissue (Poland sequence) as well as rib anomalies may cause infero-lateral displacement of nipples. Widely spaced nipples also occur in a number of other conditions, including chromosomal disorders. Accessory or multiple nipples are often an isolated finding, but may be associated with underlying renal malformation. Pectus excavatum, pectus carinatum and abnormalities of the sternum may be indicators of some bone dysplasias and other conditions.

- Cardiovascular - heart murmurs, pulses, blood pressure

  Congenital heart defects are among the most frequent isolated major malformations in newborns. They are also frequent among newborns with multiple congenital anomalies, whether as part of a specific syndrome or as associated defects. Cardiomyopathy may occur in infants of diabetic mothers and in Noonan syndrome.

  Asymmetric pulses may raise suspicion of coarctation of the aorta, which can be isolated or part of syndromes, such as Turner syndrome, or of arteriovenous malformations. Asymmetry of pulses and blood pressure are also found in Williams syndrome.

- Lungs - symmetry of breath sounds

  Asymmetry may be a clue to the presence of a lung malformation, such as a sequestered lobe, congenital cystic adenomatoid malformation or congenital diaphragmatic hernia.

- Abdomen - appearance of umbilicus, muscle tone, integrity of wall, enlarged organs or masses

  Commonly an isolated finding, a single umbilical artery may be associated with other malformations, particularly in the VATER association or trisomy 18. Abdominal wall defects such as omphalocele or umbilical hernia can be associated with Beckwith-Wiedemann syndrome, trisomy 13 or 18 and, less commonly, with other malformation syndromes. Urethral outlet obstruction sequence (prune belly) is a common cause of abdominal distension. Distension may also be a sign of obstruction within the lower gastrointestinal tract. Conversely, a scaphoid (flattened) abdomen may result from obstruction of the upper gastrointestinal tract due to esophageal or duodenal atresia. Another cause may be herniation of contents into the thorax as in diaphragmatic hernia. Palpation of the abdomen may reveal renal abnormalities, hepatomegaly or congenital tumors.

- Genitalia - size, appearance, ambiguity, palpation of testes in males

  Genital malformations are a feature of a number of syndromes, particularly in males. Hypospadias can be associated with Opitz-Frias G/BBB syndrome, Robinow syndrome, Smith-Lemli-Opitz syndrome and a number of other syndromes. Micropenis may be a feature of those syndromes cited above as well as Prader-Willi and CHARGE association. Undescended testes occur in many syndromes, such as Noonan syndrome, in addition to syndromes characterized by male hypogonadism. Ambiguous genitalia result from a variety of etiologies, including inborn errors of metabolism (i.e. congenital adrenal hyperplasia), chromosomal disorders and malformation syndromes. The newborn with ambiguous genitalia must be expeditiously examined and evaluated by endocrinology and/or genetics specialists for the purpose of sex-assignment and to prevent salt-wasting and sudden death in congenital adrenal hyperplasia.

- Anus - location and patency

  Anterior displacement of the anus is at the mild end of the spectrum of anorectal malformations. Failure to pass meconium within 24-36 hours after birth should prompt consideration of such disorders as cystic fibrosis, Hirschprung disease or anal atresia. If an anorectal malformation is found, evaluation should be done to look for additional malformations, especially those in the

VATER association (*see Appendix 1. Glossary*). Anorectal malformations also occur in a number of other syndromes, such as Townes-Brocks and FG syndromes.

- Back - symmetry, spine, sinuses or hair tufts in lumbosacral region or inter-gluteal cleft

  Asymmetry of the spine should prompt evaluation for vertebral malformations, which may be isolated or part of a syndrome. Although a presacral dimple is a common benign finding, the identification of sinuses or hair tufts should prompt evaluation for occult neural tube defects.

- Extremities - proportions, appearance, range of motion (including hips), pulses, reduction or duplication abnormalities

  Major malformations of extremities are among the most completely ascertained because of their visibility. However, careful examination should be performed to characterize the nature of the abnormalities. Reduction and duplication defects of the upper limb may be associated with other malformations and syndromes. The particular pattern of limb malformation can often assist in development of the differential diagnosis. Apparently disproportionate limbs should be measured for comparison with available normal values [Jones, 1997].

- Hands and feet - nails, creases, joints

  Hands and feet should be carefully examined for syndactyly, variations in creases, joints and nails which may be clues to the underlying etiology of other malformations. For example, single transverse palmar creases, which may occur in isolation, may also be clues to chromosomal disorders, such as Down syndrome, or to a bone dysplasia such as achondroplasia. Congenital contractures may be clues to a connective tissue disorder, such as Marfan syndrome, or a neuromuscular disorder associated with arthrogryposis. Trisomy 18 is characterized by a particular pattern of overlapping finger contractures. Lax joints and congenital dislocations are found in a number of conditions, including disorders characterized by central hypotonia and connective tissue abnormalities. Syndactyly of the second and third toe is a common inherited variation; however, in the presence of other malformations it suggests the Smith-Lemli-Opitz syndrome. Hypoplasia of the nails, particularly of the small and ring fingers, may occur in fetal alcohol syndrome, fetal hydantoin syndrome or the ectodermal dysplasias.

- Neurological - tone, response, alertness, reflexes

  Abnormal newborn neurological examination is seen in a number of syndromes which include brain malformations and/or brain dysfunction and in association with various inborn errors of metabolism. Hypotonia should prompt evaluation for a neuromuscular or central nervous system disorder. In association with joint laxity, hypotonia may suggest congenital Marfan syndrome or Ehlers-Danlos syndrome. Further, hypotonia may be the cardinal manifestation of chromosomal disorders such as Down syndrome as well as many inborn errors of metabolism involving diverse metabolic abnormalities. The neonate's responsiveness and alertness are reflections of the adequacy of central nervous system (CNS) function. Somnolence, poor response and poor feeding are important symptoms which should prompt consideration of CNS malformation or dysfunction in the neonate. Alterations of reflexes may also be significant in the neonate. Increased reflexes may indicate CNS hyperirritability, a sign of spinal cord compression in certain skeletal dysplasias such as achondroplasia. Decreased reflexes may suggest myopathies or neuropathies such as Werdnig-Hoffman type spinal muscular atrophy.

Initial Impression and Differential Diagnosis

A dynamic interactive process incorporating the history and physical examination should lead to an initial diagnostic impression and a differential diagnosis. These will guide the selection of initial tests, the content of initial counseling of the family and development of an

immediate plan for management, which can be modified as new information is synthesized. The initial impression should fit into one of three categories:

- Single (isolated) malformation

  If it is concluded that a common, isolated malformation is present, specific diagnostic testing to clarify the extent and nature of the malformation and to generate an appropriate management strategy should be pursued. Specific genetic testing (e.g. chromosomal analysis) may not be required. A long range comprehensive plan for management should be developed.

- Multiple malformations, recognizable pattern (syndrome identification)

  When a specific diagnosis is recognized, the plan for confirmatory testing and evaluation (if appropriate), family counseling and management should be based on the diagnosis. If the condition is not familiar to the clinician, available resources should be accessed, and specialty consultation should be considered.

- Multiple malformations, pattern not recognized

  When the constellation of malformations is not recognized as a known syndrome or pattern, diagnostic tests such as routine or high resolution karyotyping should be pursued to assist diagnosis. Consultation with medical geneticists or other appropriate specialists should occur. Such consultation can help determine the course of the diagnostic evaluation. The specialist may be able to make a diagnosis or may suggest additional tests which may lead to a diagnosis.

Diagnostic evaluation

Features of the clinical presentation should guide the clinician in the selection of diagnostic tests intended to aid or confirm diagnosis. Such tests are of particular value when no syndrome or pattern is recognized or to confirm a diagnosis made on a clinical basis. Single (isolated) malformations or syndromes which are recognized on a clinical basis may not require additional genetic diagnostic tests. On the other hand, diagnostic tests may be of particular value when a syndromic pattern is not recognized. In many cases such tests yield information which can facilitate risk assessment for genetic counseling. The tests described below are those most commonly employed; other tests might apply in a given clinical situation. A "shotgun" approach should be avoided; the results of tests performed in a reasoned sequential order may guide selection of more specific evaluations. Consultations with specialists in pertinent fields may clarify diagnostic possibilities. Medical genetics consultation should be sought for assistance in the diagnostic evaluation, for interpretation of diagnostic tests, when needed to confirm a questionable diagnosis or to assist in diagnosis when one is not apparent. It is important to discuss the possible implications of genetic testing, including those whose results will have implications for relatives. The primary care provider may also wish to refer in cases where detailed genetic counseling is needed, particularly in complex situations (*see Appendix 4 for Genetic Service Providers in New York State and Appendix 5 for State Genetics Coordinators*). Diagnostic tests which should be considered include:

- Diagnostic imaging studies

  Targeted radiographs of areas with defined or suspected malformation should be obtained to clarify the extent or nature of the abnormalities. In the presence of apparent skeletal disproportion, there should be a "genetic skeletal survey" including radiographic views of the skull, spine, ribs, long bones, pelvis, hands and feet. A single whole body radiograph ("babygram") has limited utility in the term infant because of lack of fine detail.

Other skeletal imaging, computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US) should not be considered routine, but should be employed when appropriate and based on the differential diagnosis.

- Chromosome analysis

A G-banded (Giemsa banded) chromosome analysis should be obtained on the newborn with two or more major malformations. High resolution (>550 band level) banding should be done to exclude small structural chromosome rearrangements if there is high clinical suspicion of a chromosome abnormality, even when a prenatal specimen revealed a normal chromosome constitution.

Newborns with a single congenital anomaly, in general, do not require a chromosomal analysis. However, newborns with a single major malformation or multiple minor malformations who are also small-for-dates [Khoury et al, 1988; Mili et al, 1991] or those with minor anomalies in addition to a single major malformation should have chromosome analyses.

It is important to realize that a normal chromosome analysis does not eliminate the possibility of a genetic disorder. Most Mendelian disorders are not detected by chromosome analysis. Some contiguous gene syndromes (microdeletions) such as those associated with Williams syndrome and DiGeorge/velocardiofacial syndrome are not detected by routine chromosome analysis and require specific molecular cytogenetic techniques, e.g. FISH analysis.

- Other genetic tests

Fragile X syndrome is not typically associated with malformations apparent in the newborn. For this reason, although Fragile X analysis is of value in specific situations, it is not useful in the evaluation of the newborn with malformations.

Biochemical or metabolic testing is of value in certain situations (*see Table 5*) where signs and symptoms suggest an inborn error of metabolism. For example, when signs of Smith-Lemli-Opitz syndrome are present, testing should be done to detect low serum cholesterol or elevated 7-dehydrocholesterol [Tint, 1993]. When ambiguous genitalia are present, quantification of adrenocorticosteroids is necessary to evaluate a child for congenital adrenal hyperplasia [Allen et al, 1997].

Table 5. Situations Suggesting the Need for Metabolic Testing in the Newborn with Malformations:

Selected Clinical Findings	Selected Laboratory Findings	Selected Radiologic Findings
Ambiguous genitalia	Metabolic acidosis	Punctate calcifications
Enlarged fontanelle	Abnormal liver function tests	Severe osteopenia
Seizures	Persistent hyperbilirubinemia	
Severe hypotonia	Hyperammonemia	
Cataracts	Hypocholesterolemia	
Coarse facies	Hypoglycemia	
Hepatosplenomegaly		
Lethargy or coma		
Persistent vomiting		
Unusual odor		

Molecular genetic tests are occasionally indicated to make or confirm specific diagnoses, such as microdeletion syndromes. Specific molecular genetic tests are available for a number of multiple malformation syndromes, but should be selected based on the differential diagnosis. (*Table 6 lists multiple malformation syndromes for which molecular tests may be available*.)

Table 6. A Sampling of Congenital Malformation Syndromes for which Specific Molecular Tests may be Available

SYNDROME	MOLECULAR TEST
MICRODELETION SYNDROMES	
Williams	*ELN* (elastin)
Velocardiofacial/DiGeorge	Microdeletion within 22q11
Miller-Dieker	Microdeletion within 17p13.3
CRANIOSYNOSTOSIS SYNDROMES	
Apert and Crouzon	*FGFR2*
Pfeiffer	*FGFR1*
Saethre-Chotzen*	*Twist* or *FGFR3*
MALFORMATION SYNDROMES	
Treacher Collins	*Treacle*
Waardenburg*	*PAX3* or *HOX10*
Alagille	*Jagged*
BONE DYSPLASIAS	
Achondroplasia or thanatophoric dysplasia	*FGFR3*
Osteogenesis Imperfecta*	*COL1A1* or *COL1A2*
Spondyloepiphyseal dysplasia congenita	*COL2A1*

** Linkage to two different genes has been found in different families*

Working diagnosis

In many instances a specific diagnosis can be established in the newborn period. When a specific diagnosis cannot be established, a working diagnosis is necessary, in order to implement a plan for immediate and long term management. A working diagnosis is based on the history, physical examination and available diagnostic evaluations. Part of the diagnostic process should be to search the many available library and electronic resources for further assistance (*see Appendix 3*). Consultation may also be required at this point.

The working diagnosis is not necessarily the final diagnosis, which may be arrived at over time and after diagnostic testing. Use of reference material can assist periodic review of the working diagnosis as the patient's clinical course unfolds. Genetic counseling with only a working diagnosis is complex and difficult in terms of communication and content. It may be particularly helpful to consult with a genetics professional before venturing into this area.

Counseling the family

Counseling Principles

The approach taken in counseling the family of a newborn with congenital anomalies sets the stage for the family's adaptation to their infant and for future interactions with the family [Krahn, 1993; Klein, 1996; Walker, 1997]. Counseling in this situation involves the same principles of communication as are appropriate for other complex medical diagnoses, including respect for family privacy, confidentiality and autonomy, sensitivity to cultural, ethnic, language and religious issues and maintenance of a supportive environment. Genetic counseling is a specific component of counseling for the family of a newborn with malformations.

Genetic counseling addresses the diagnosis and the possible role of genetic factors, medical aspects of the condition, risk of recurrence and options for dealing with those risks, in order to enable families to make the best adjustment and most appropriate decisions for their newborn and family [Walker, 1997].

Supportive setting

It is important to establish rapport, through a family-centered, non-judgmental approach, taking into account the family's knowledge of the diagnosis [Ptacek, 1996], expectations of the counseling session, and level of receptivity. A quiet, private location should be selected and, optimally, both parents should be invited to attend along with other family members they designate [Bocian, 1978; Ives, 1979; Krahn, 1993; Sharp, 1992; Walker, 1996]. Some families may wish to invite others they perceive to be part of their support system, which may include clergy, social workers or friends.

In developing rapport with the family, it is important to establish a plan for initial and ongoing emotional support. The health care provider should recognize and acknowledge the emotional impact on the family of a newborn with a malformation. At an initial session, the family is likely to be in a state of considerable anxiety, attempting to cope with the situation by invoking denial, guilt, anger, intellectualization and/or other aspects of grief in response to their perceived loss of the expected "perfect baby" [Bocian & Kaback, 1978; Sharp, 1992; Davis, 1995; Walker, 1996; McCubbin & Patterson, 1982]. It is very common (although often unexpressed or unrecognized) for one or both parents to feel that they are somehow responsible for their baby's problems. Relief of guilt and reassurance as to the normalcy of their responses should be a primary goal of the initial interaction [Klein, 1996; Walker,1996], and the family may need several sessions to facilitate their adaptation to the situation.

Definition of Genetic Counseling

Genetic counseling is a communication process which deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. The process of genetic counseling involves an attempt by one or more appropriately trained individuals to help the affected individual or family to:

(1) comprehend the medical facts, including the diagnosis, probable cause of the disorder, and the available management;

(2) appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives;

(3) understand the alternatives for dealing with the risk of recurrence;

(4) choose the course of action which seems to be appropriate in view of their risk, their family goals, and their ethical and religious standards, and to act in accordance with that decision; and

(5) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

(From the Ad Hoc Committee on Genetic Counseling of the American Society of Human Genetics, Am. J. Human Genetics 27: 240-242, 1975.)

Content

At the outset of counseling, it should be conveyed that the initial session represents the beginning of a communication process intended to gather medical information, explain the medical facts and answer questions. Availability for future communication should be assured. Information should be given in a staged fashion, with multiple interactions over time, at a pace responsive to the family's need [Ptacek, 1996; Shokeir, 1979]. In general, limited technical information should be provided at the first session or when one first meets with the

family. Many families have trouble with assimilation when they hear distressing medical information; others intellectualize technical information as a component of their grief reaction [Bocian & Kaback, 1978; Shokeir, 1979]. Brief, concise, finite answers should be provided, but detailed and lengthy explanations of pathogenesis should be avoided.

The family should be given the basic facts, realistic expectations and possible prognoses along with immediate treatment plans and options. Counseling should include a thorough discussion of the current status of the newborn; whether or not a diagnosis has been established; and the need for further consultation or evaluation. When delivering information regarding a neonate, particularly when the diagnosis is unknown, guarded optimism is often justified [Ptacek, 1996].

Subsequent sessions should focus on the means of helping the child achieve his/her full potential, available community resources and family adaptation skills [Krahn, 1993; Sharp, 1992]. Options for medical, surgical and educational therapy should be explored and health insurance needs addressed. Repetition of difficult news or complex information at more than one session may be necessary to assure its assimilation by a family which is overwhelmed [Ptacek, 1996; Walker, 1996]. Some families may benefit from referral to a genetic counselor, mental health professional, social worker, clergy, or other support person or group.

Where to find Genetic Support Groups

Alliance of Genetic Support Groups
4301 Connecticut Avenue, NW, Suite 404
Washington, DC 20008-2304
(800) 336-GENE (4363)
e-mail: info@geneticalliance.org
<http:// www.geneticalliance.org/>

The National Organization for Rare Disorders, Inc.
P.O. Box 8923
New Fairfield, CT 06812-8923
(203) 746-6518 Fax (203) 746-6481
(800) 999-6673
<http://www.pcnet.com/~orphan>

March of Dimes Resource Center
1275 Mamaroneck Avenue
White Plains, NY 10605
(888) MODIMES (663-4637)
e-mail: resourcecenter@modimes.org
<http://www.modimes.org/rc/help.htm>

Given the wide variability of many malformations and malformation patterns, information about prognosis should be qualified by its degree of certainty. It should be recognized that the biomedical literature may not provide a balanced perspective, because of bias of ascertainment toward the more severely affected; individual affected children may have better or worse outcomes. When a specific diagnosis is not achieved or is uncertain, counseling should address reasons for this. Steps which will be taken in an attempt at resolution should be described (see "Dealing with Uncertainty" below). Variability in outcome should be stressed when appropriate, and families offered a reasonable level of hope. Referral to appropriate genetic support groups may help the family to recognize the variable outcomes possible (*see sidebar for sources of information*).

Recurrence risk and prenatal diagnosis issues should be fully discussed over time but should not dominate the first encounter. It is appropriate in the first session to address recurrence risk, if known, and to state that unaffected offspring in a subsequent pregnancy are possible. Detailed discussion of prenatal diagnosis and reproductive options should be deferred to a subsequent session or to professionals (such as genetic counselors) with experience in these sophisticated and complex technologies.

Patient Record

The patient record regarding the newborn with one or more malformations should contain comprehensive documentation. In addition to information about the history and physical examination, the patient's file should include the following:

- Documentation of positive and negative findings

  The relevance of specific details of the history and physical examination may become apparent only in retrospect when the infant presents for care at a later age. Clear initial documentation is of particular value in the case of malformations for which therapeutic intervention (such as surgery) is planned and to document clinical findings which may change with age. Clinical photography is an important adjunct to clinical descriptions in the medical record but should not be considered a substitute for careful description. Clinical photographs are invaluable, particularly to document changes over time and for "curbside" consultations.

- Diagnostic considerations

  It is important to document the diagnostic considerations and the underlying findings upon which these conclusions were based. As new information becomes available, any revision of the diagnosis should be documented.

- Management plan for further evaluation and treatment

  Coordination of care for infants with complex needs is facilitated by having a documented plan accessible to other health care providers.

- Issues discussed in counseling

  Documentation of topics covered in family counseling sessions forms the basis for written communication to the family and to others involved in their care.

Considerations about etiology should be carefully documented and based on available facts, rather than speculation. Privacy and confidentiality of the medical record must be assured to the maximum extent possible.

Longitudinal Care and Case Management

The physician assuming ongoing care of the patient should, in most instances, be the primary care physician, assisted by appropriate specialty consultation [American Academy of Pediatrics, 1996]. Many helpful documents regarding common malformations and syndromes are available to the primary care provider (*see Appendix 3, General Resources*). In some instances, practical considerations for optimal management may require the services of specialists or comprehensive treatment centers for case management of complex conditions.

Letters to families should include:

- Patient's name, diagnosis and means by which diagnosis was reached
- Brief summary of consultation and recurrence risk for family and their close relatives
- Availability of prenatal diagnostic testing
- Primary care provider's availability for ongoing discussion or referral
- Information on support groups and community resources

For the newborn with multiple malformations, a summary of relevant medical facts, test results, differential and working diagnoses and a treatment plan should be

available in the chart and to the family as they interact with other health care providers. In some instances, it is also appropriate to provide the family with a summary letter outlining the diagnosis and recurrence risks, written in understandable language with minimal jargon. Written documentation can serve as a permanent summary of counseling issues which can be used for future reference; summaries are also useful sources of information for other health care providers and family members [Ptacek, 1996; Klein, 1996].

Dealing with Uncertainty

Among the more perplexing and stressful situations for families and health care providers is the lack of a specific diagnosis. In these instances it is inadvisable to attempt to assign risk and specific prognostication is often not possible. Long-term follow-up may be critical to establish a diagnosis not apparent at birth which depends upon the evolution of a specific behavioral or physical phenotype. For example, in conditions such as Williams, Prader-Willi and velo-cardio-facial syndromes, the appropriate diagnosis may not be apparent for months or years. Longitudinal observation may offer the opportunity for clinical reassessment, review of new findings, synthesis of new literature and continued patient management and family counseling. *Often it is better for an infant or child to remain undiagnosed until there is a reasonable degree of medical certainty regarding the nature of the condition rather than to retain a poorly fitting diagnosis.* In light of the rapidity with which new genetic knowledge and technical advances are occurring, the option of consultation with a specialist in medical genetics may be of particular value. *(See Appendix 4 for New York State genetic service providers and Appendix 5 for State Genetics Coordinators.*)

Further Recommendations and Conclusions

The diagnosis and management of newborns with one or more congenital anomalies can be complex and at times requires coordination of multiple disciplines. The primary care provider should be aware of the following:

1. Every effort should be made to obtain an etiologic diagnosis in the newborn with one or more malformations. A specific diagnosis will enable the physician to understand the immediate and long term needs of the patient, mobilize the resources required to optimize outcome and provide information regarding education, genetic recurrence risks and support to the family.

2. Assignment of a final diagnosis may require ongoing observation and the incorporation of newly developed techniques as new data become available. The medical geneticist may serve as an important resource under such circumstances.

3. Staging of communication and information according to the family's needs is essential.

4. Families should receive information about the diagnostic process and diagnosis in a manner that is linguistically appropriate and ethnically and culturally sensitive. This includes, when known, information on natural history, prognosis, genetic recurrence risks and available resources. Such information should be transmitted in person and whenever possible in written form as well.

5. The primary care provider must be aware of some of the extensive resources available (see Appendices for examples) and use them when appropriate. In addition to the standard medical literature, this includes syndrome/birth defect compendia and databases, support group publications, information from public health agencies and other relevant sources specific to the condition.

6. Primary care providers should recognize their role in helping the family adjust to the impact of the birth of a child with a congenital disorder. Ongoing care and support are best provided by the primary health care provider, with assistance from the medical genetics specialist or other specialists when needed.

7. The primary care provider must ensure the confidentiality and privacy of genetic information.